isotypes is less than the number of nucleotides between the gene segments encoding human mu and said human gamma isotype in the human germline; and

collecting heterologous human gamma immunoglobulins which bind to the pre-selected antigen.

REQUEST FOR INTERFERENCE

Applicants request that an interference be declared between this application and the '806 patent [37 C.F.R. § 1.607(a)(1)].

The '806 patent issued on August 13, 1996 from application 07/990,860, filed December 16, 1992. The earliest effective filing date to which the '806 patent could even arguably be entitled is August 29, 1990.*

As discussed below, claim 45 of this application is entitled to claim the benefit of the January 12, 1990 filing date of parent application 07/466,008 ("the '008 application").** Applicants' earliest effective filing date,

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* The '860 application from which the '806 patent issued claims the following ancestry. It is a continuation-in-part of copending United States application 07/904,068, filed June 23, 1992, which is a continuation-in-part of copending United States application 07/853,408, filed March 18, 1992, which is a continuation-in-part of United States application 07/810,279, filed December 17, 1991, now United States patent No. 5,569,825, which is a continuation-in-part of United States application 07/575,962, filed August 31, 1990, now abandoned, which is a continuation-in-part of United States application 07/574,748, filed August 29, 1990, now abandoned. The '806 patent also claims priority under 35 U.S.C. § 119 to PCT/US91/06185, which corresponds to United States application 07/834,539, filed February 5, 1992.

** This application is a continuation-in-part of copending United States application 08/430,938, filed April 27, 1995, which is a continuation-in-part of copending United States application 08/234,145, filed April 28, 1994, which is a continuation-in-part of copending United States application 08/112,848, filed August 27, 1993, which is a continuation-in-

(continued...)

thus, is more than seven months before the earliest possible effective date of the '806 patent.* Accordingly, applicants are presumptively the first inventors of the subject matter of claim 45 of this application and claim 1 of the '806 patent and should be designated Senior Party in the requested interference [37 C.F.R. § 1.601(m)].

1. The Proposed Count

Applicants present the following Proposed Count 1 for the purposes of this interference [37 C.F.R.§ 1.607(a)(2)].

Proposed Count 1

A method for producing heterologous immunoglobulins from a transgenic mouse, the method comprising:

> contacting said transgenic mouse with a pre-selected antigen, said transgenic mouse having a genome comprising germline copies of at least one transgene having human sequences V_H segment genes, human D segment genes, and human J_H segment genes, wherein the transgene undergoes isotype switching from a transgene-encoded mu isotype to a transgene-encoded downstream human gamma isotype *in vivo*, wherein the number of nucleotides between the gene segments within the transgene that encode said mu and said human gamma isotypes is less than the number of nucleotides between the gene segments encoding human mu and said human gamma isotype in the human germline; and
>
> collecting heterologous human gamma immunoglobulins which bind to the pre-selected antigen.

** (...continued)
part of copending United States application 08/031,801, filed March 15, 1993, which is a continuation-in-part of United States application 07/919,297, filed July 24, 1992, now abandoned, which is a continuation-in-part of United States application 07/610,515, filed November 8, 1990, now abandoned, which is a continuation-in-part of United States application 07/466,008, filed January 12, 1990, now abandoned. This application also claims priority under 35 U.S.C.§ 119 to PCT application PCT/US96/05928, filed April 29, 1996.

* Because applicants' earliest effective filing date is before the earliest possible effective filing date of the '806 patent, 37 C.F.R.§ 1.608 does not apply here.

Claim 1 of the '806 patent corresponds exactly to Proposed Count 1 and is the broadest claim of the '806 patent [37 C.F.R.§ 1.606].

2. Applicants' Claim 45 Corresponds To The Proposed Count

Applicants' claim 45 is identical to and thus corresponds exactly to Proposed Count 1 [37 C.F.R. §§ 1.601(f) and 1.607(a)(4)].

3. Claim 45 Is Patentable To Applicants

A. Claim 45 Is Presumptively Free of Prior Art

The issuance of claim 1 in the '806 patent carries the presumption that the claim is free of prior art. For the same reason, claim 45 is patentable to applicants.

B. Claim 45 Is Supported By Applicants' Disclosure

This application expressly incorporates by reference the disclosure of the '008 application, filed January 12, 1990 (see specification, page 1, lines 14-16).

To simplify this paper, applicants will, thus, apply the terms of claim 45 to the disclosure of the '008 application. In that way, applicants simultaneously demonstrate support for the claim in this application and their entitlement to the benefit of the January 12, 1990 filing date of the '008 application for it [37 C.F.R. § 1.607(a)(5)]. (Applicants have enclosed a copy of the '008 application as Exhibit B.)

The '008 application supports each of the elements of claim 45:

1. "A method for producing heterologous immunoglobulins from a transgenic mouse, the method comprising:" (Preamble)

See, the '008 application, throughout.

2. "contacting said transgenic mouse with a pre-selected antigen"

The '008 application is directed to methods and compositions for the production of xenogeneic antibodies in a non-human host in response to immunization with an antigen of interest. See, for example, the '008 application:

page 3, lines 23-26: "Xenogeneic specific binding proteins are produced in a non-primate viable mammalian host by immunization of the mammalian host with an appropriate immunogen";

page 7, lines 3-8: "Thus, by obtaining a subset of the known V region genes of the human heavy and light chain Ig loci rather than the entire complement of V regions, the transgenic host may be immunized and be capable of mounting a strong immune response and provide high affinity antibodies";

page 13, lines 23-26: "Such a host strain, by immunization with specific antigens, would respond by the production of mouse B-cells producing specific human antibodies";

page 14, lines 27-30: "Where the mammalian host has been immunized with an immunogen, the resulting human antibodies may be isolated from other proteins by ...";

page 24, lines 1-4: "In accordance with the above procedures, the antigenic or chimeric non-primate host,

particularly mouse host, may be produced which can be immunized to produce human antibodies"; and

claim 1: "A method for producing xenogeneic primate antisera or antibody analog in a mammalian non-primate host, said method comprising: immunizing said host with an immunogen" (page 26).

3. "said transgenic mouse having a genome comprising germline copies of at least one transgene having human V_H segment genes human D segment genes, and human J_H segment genes."

The '008 application discloses, throughout, the use of a transgene encoding a human immunoglobulin heavy chain. That transgene comprises human V, human D and human J segments. The construction of a transgene containing those human segments is also expressly described. See, for example, the '008 application:

page 3, line 37 to page 4, line 4: "the mammalian host ... may have an entire immunoglobulin locus of the host substituted by a portion or an entire xenogeneic immunoglobulin locus, or may have a xenogeneic immunoglobulin locus inserted into a chromosome of the host cell";

page 5, lines 6-10: "The complete human heavy and light chain genes are reconstructed in an appropriate eukaryotic microorganism and the resulting DNA fragments can be introduced into pronuclei of fertilized mouse oocytes or embryonic stem cells";

page 5, line 28 to page 6, line 2: "These strategies are based on the known organization of the immunoglobulin chain loci in a number of animals ... In the human, the

immunoglobulin heavy chain locus ... comprises a large cluster of variable region genes (V_H), the diversity (D) region genes, followed by the joining (J_H) region genes";

page 7, lines 9-15: "In this manner, relatively small DNA fragments of the chromosome may be employed, for example, a 670 kb fragment of IgH_{hu} locus is shown in Figure 1b." (That 670 kb fragment contains V, D and J genes and a complement of constant region genes.)

page 20, line 1 to page 23: describes the production of a DNA vector containing a fragment of the human heavy chain locus which includes V, D, and J segments; and

claim 7: "A method according to claim 1, wherein said host comprises at least a functional portion of human immunoglobulin loci for a heavy chain" (page 27).

4. "wherein the transgene undergoes isotype switching from a transgene-encoded mu isotype to a transgene-encoded downstream human gamma isotype in vivo."

The '008 application describes the production of IgG (gamma isotype) antibodies. See, for example, the '008 application:

page 4, lines 24-25: "The antibodies may be of any isotype, e.g. IgA, D, E, G [gamma] or M [mu] or subtypes within the isotype."

Further, the '008 application is directed to obtaining high affinity antibodies. See, for example, the '008 application:

page 6, lines 36-37: "In order to obtain a broad spectrum of high affinity antibodies, ..."

page 7, lines 6-8: "the transgenic host may be immunized and be capable of mounting a strong immune response and provide high affinity antibodies".

High affinity antibodies are predominantly secreted antibodies and typically include IgG antibodies.

And, the '008 application states that protein A may be used to isolate the xenogeneic antibodies of the invention. See, the '008 application:

page 14, lines 27-31: "Where the mammalian host has been immunized with an immunogen, the resulting human antibodies may be isolated from other proteins by using an affinity column, having Fc binding moiety, such as protein A, or the like."

Protein A is well-known to be a specific binding partner for IgG antibodies.

The '008 application also expressly claims the production of two types of antibodies, a surface immunoglobulin on B cells, i.e, an IgM antibody, and a second antibody specific for the immunogen, e.g., an IgG antibody. See, the '008 application:

claim 1: "said host mounts an immune response to said immunogen and produces plasma cells, B-cells have surface immunoglobulin specific for said immunogen and antibodies specific for said immunogen" (page 26).

Finally, the entire disclosure of the '008 application is directed to the production of antibodies, particularly human antibodies, for therapeutic use. See, the '008 application, page 1, line 19 to page 3, line 1, which describes the need for antibodies that may be administered repetitively to humans in the case of chronic diseases.

The '008 application expressly discloses that the antibodies of the invention are produced by immunizing a non-human host that is incapable of producing endogenous antibodies with an antigen of interest. See, for example, the '008 application: page 3, lines 26-28; page 3, line 34 to page 4, line 5; page 5, lines 3-5 and lines 11-20; page 7, lines 17-22, lines 25-28 and lines 33-37; page 8, line 1 to page 9, line 37; page 13, lines 8-23; pages 27-28, claims 7, 8, 14, 16 and 17; page 30, Abstract lines 8-12 (disclosing the use of a transgenic animal that is incapable of producing endogenous antibodies).

Because the host animal is incapable of producing endogenous antibodies, any antibodies produced in the animal are encoded by the transgene.

The '008 application states that in response to immunization, the "host mounts an immune response to said immunogen and produces plasma cells, B cells have surface immunoglobulin specific for said immunogen and antibodies specific for said immunogen" (see, the '008 application, claim 1). See also, the '008 application: page 4, lines 11-14; page 7, lines 6-8; page 13, lines 23-29; page 14, lines 27-31; page 24, lines 1-5; page 26, claim 1; and page 30, lines 8-12 (stating that the transgenic animal will mount a strong immune response, producing plasma cells, antibody producing B-cells and high affinity antibodies).

On January 12, 1990, when applicants filed the '008 application, the mechanism of antibody production in response to antigen stimulation was known to require first, the production of surface IgM antibodies on B cells, followed by the production of secreted, higher affinity antibodies specific for the antigen. If antibodies cannot be made endogenously, they must

be expressed from the transgene. If the host produces surface immunoglobulin on B cells, then the transgene produces IgM antibodies. If the host also produces high affinity antibodies specific for the immunogen, the transgene also produces, e.g., IgG antibodies.

5. "wherein the number of nucleotides between the gene segments within the transgene that encode said mu and said human gamma isotypes is less than the number of nucleotides between the gene segments encoding said human mu and said human gamma isotype in the human germline;"

The '008 application describes embodiments in which the transgenic animal comprises a transgene with a portion of a xenogeneic immunoglobulin heavy chain locus. See, the '008 application:

page 3 line 34 to page 4, line 2: "Thus, the mammalian host will comprise at least one xenogeneic constant region capable of being spliced to a functional J region of the immunoglobulin locus, may have an entire immunoglobulin locus of the host substituted by a portion or an entire xenogeneic immunoglobulin locus";

page 8, lines 24-28: "The number of transformation steps may be reduced by providing at least a fragment of the human immunoglobulin subunit locus for homologous recombination with the analogous endogenous immunoglobulin";

claim 7: "A method according to claim 1, wherein said host comprises at least a functional portion of human immunoglobulin loci for a heavy chain and a light chain" (page 27);

claim 8: "A transgenic non-primate mammal comprising a genome comprising: at least a functional portion of human

immunoglobulin loci for at least a portion of the heavy chain" (page 27);

page 28, claims 14, 16 and 17: recites a transgenic mouse or transgenic non-primate mammal "comprising a genome comprising: ... at least a functional portion of human immunoglobulin loci for a heavy chain".

The '008 application also discloses a transgene in which the number of nucleotides between mu and gamma are less than in the human germline. The application discloses a transgene in which the functional portion of the heavy chain comprises "at least one constant region" (see claim 12, page 27). The '008 application further states that the disclosed strategies for producing the xenogeneic antibodies are based on knowledge of the organization and location of exons encoding domains and splice sites in the immunoglobulin loci. See, the '008 application, page 5, lines 28-33:

> "These strategies [for producing the transgenic animal of the invention] are based on the known organization of the immunoglobulin chain loci in a number of animals, since the organization, relative location of exons encoding domains, location of splice sites and transcriptional elements, is understood to varying degrees".

And, the '008 application states that using the methods of the invention, any gamma subtype may be produced (see, page 4, lines 24-25).

Finally, on January 12, 1990, when applicants filed the '008 application, it was known that the segments encoding the gamma subtypes (gamma-1 to -4) are not contiguous. They are dispersed within the immunoglobulin heavy chain constant region. See, for example, J.E. Berman et al., "Content And Organization Of The Human Ig V_H Locus: Definition of Three New V_H Families and Linkage to the Ig C_H Locus," *EMBO J.*, 7, pp. 727-738 (1988);

M.H. Hofker et al., "Complete Physical Map of the Human Immunoglobulin Heavy Chain constant Region Gene Complex," *Proc. Natl. Acad. Sci.*, 86, pp. 5567-5571 (1989) (copies enclosed as Exhibits C and D, respectively).

A transgene encoding a gamma-2 antibody, thus, may comprise, e.g., two constant region segments, mu and gamma-2, which are not contiguous in the human germline. Such a transgene has fewer nucleotides between the transgene-encoded mu and the transgene-encoded gamma segments than in the human germline.

6. "and collecting heterologous human gamma immunoglobulins which bind to said preselected antigen."

The '008 application is directed to the preparation and collection of high affinity xenogeneic (heterologous) antibodies, particularly human antibodies. See, the '008 application:

page 4, lines 30-32: "For the most part, mice have been used for the production of B-lymphocytes for immortalization for the production of antibodies";

page 13, lines 23-29: "Such a host strain, by immunization with specific antigens, would respond by the production of mouse B-cells producing specific human antibodies, which B-cells could be fused with mouse myeloma cells or be immortalized in any other manner for the continuous stable production of human monoclonal antibodies";

page 14, lines 17-31: describes the production of hybridomas from B cells of immunized, transgenic mice,

obtaining ascites and the isolation of the heterologous antibody;

page 14, lines 27-31: "Where the mammalian host has been immunized with an immunogen, the resulting human antibodies may be isolated from other proteins by using an affinity column"; and

page 24, lines 1-27: states that B cells from immunized transgenic mice may be immortalized for the continuous production of desired heterologous antibodies.

4. Patentee's Claims That Correspond To The Proposed Count

Patentee's claim 1 corresponds exactly to Proposed Count 1. Patentee's claims 2-14 correspond substantially to Proposed Count 1 [37 C.F.R.§ 1.607(a)(4)].

a. Claim 1

Claim 1 corresponds exactly to Proposed Count 1.

Claim 1 recites:

> 1. A method for producing heterologous immunoglobulins from a transgenic mouse, the method comprising:
>
> contacting said transgenic mouse with a pre-selected antigen, said transgenic mouse having a genome comprising germline copies of at least one transgene having human sequences V_H segment genes, human D segment genes, human J_H segment genes, wherein the transgene undergoes isotype switching from a transgene encoded mu isotype to a transgene-encoded downstream human gamma isotype *in vivo*, wherein the number of nucleotides between the gene segments within the transgene that encode said mu and said human gamma isotypes is less than the number of nucleotides between the gene segments encoding human mu and human gamma isotype in the human germline; and,
>
> collecting heterologous human gamma immunoglobulins which bind to said preselected antigen.

b. Claim 2

Claim 2 corresponds substantially to Proposed Count 1.

Claim 2 recites:

> 2. A method according to claim 1, wherein the transgenic mouse has a genome comprising germline copies of at least one human light chain immunoglobulin transgene, wherein said light chain is a kappa light chain.

Proposed Count 1 recites a method for producing heterologous immunoglobulins, which are made up of heavy and light chains. The method of claim 2, differs from Proposed Count 1 only in specifying that the light chain is a kappa light chain. It was well known in 1990 that human immunoglobulins contain one of two types of light chain and that approximately 60% of human immunoglobulins contain the kappa type. Thus, the method of claim 2 is not patentably distinct over Proposed Count 1.

c. Claim 3

Claim 3 corresponds substantially to Proposed Count 1. Claim 3 recites:

> 3. A method according to claim 1, wherein the transgene is an unrearranged human heavy chain transgene comprising two human V_H gene segments, eight human D gene segments, six human J_H gene segments, a human J-mu enhancer, a human mu switch region, a complete set of human gamma C_H exons, and a heavy chain 3' enhancer, and wherein said unrearranged human heavy chain transgene lacks non-human V_H gene segments, nonhuman D gene segments, and nonhuman J_H gene segments, and wherein B lymphocytes of said transgenic mouse rearrange said unrearranged human heavy chain transgene by V-D-J joining to produce a V-D-J gene joined in-frame encoding a human heavy chain variable region which is alternately expressed in polypeptide linkage by isotype switching to the mu and gamma constant region encoded on said transgene.

The method of Proposed Count 1 uses a human transgene containing "human V segment genes, human D segment genes and human J segment genes". It is, thus, an unrearranged transgene. The transgene of Proposed Count 1 undergoes isotype switching from a transgene encoded mu isotype to a transgene encoded gamma isotype in vivo. Thus, it contains complete sets of mu and gamma exons and the sequences required for switching.

The method of Proposed Count 1 further comprises the steps of contacting an animal containing the transgene with an

antigen and collecting human gamma immunoglobulins that bind to the antigen. A "human gamma immunoglobulin" must lack non-human V, D or J segments. Further, it is well known in the art the steps recited in Proposed Count 1 require (1) rearrangement of the transgene by V-D-J joining in B lymphocytes; (2) the production of a V-D-J gene joined in-frame encoding a human heavy chain variable region; and (3) expression peptide linkage to the transgene encoded constant region genes.

Claim 3, thus, differs from Proposed Count 1 only in the recitation of two V segments, eight D segments, and 6 J segments, a J-mu enhancer and a heavy chain 3' enhancer. None of those recitations renders claim 3 patentable over Proposed Count 1. Accordingly, claim 3 corresponds to Proposed Count 1.

d. Claim 4

Claim 4 corresponds substantially to Proposed Count 1. Claim 4 recites:

> 4. A method according to claim 3, wherein said V-D-J gene joined in-frame encodes a human heavy chain variable region expressed in polypeptide linkage to the human gamma constant region encoded on said transgene.

Claim 4 adds nothing to claim 3. It is directed to one of the alternatives recited in claim 3 -- expression of the heavy chain variable region in peptide linkage to the gamma constant region. Accordingly, Claim 4 corresponds to Proposed Count 1 for the same reasons that claim 3 does.

e. Claims 5-7

Claims 5-7 correspond substantially to Proposed Count 1. Claims 5-7 recite:

> 5. A method according to claim 3, wherein said V-D-J gene joined in-frame comprises a human DIR2 gene sequence.
>
> 6. A method of claim 3, wherein said unrearranged human heavy chain transgene comprises the NotI insert of pHC1.

7. A method of claim 3, wherein said transgene comprises human VH gene segments VH251 and VH105.

Claim 5 differs from claim 3 only in the recitation of a known and previously isolated human D segment gene, DIR2 (see, Y. Ichihara et al., "Organization of Human Immunoglobulin Heavy Chain Diversity Gene Loci," *EMBO J.*, 7, pp. 4141-4150 (1988)) (copy enclosed as Exhibit E).

Claim 6 differs from claim 3 only in the recitation of a specific example of the transgene containing the recited components.

Claim 7 differs from claim 3 only in the use of known and previously isolated human V segment genes, V_{H251} and V_{H105} (see, C.G. Humphries et al., "A New Human Immunoglobulin V_H Family Preferentially Rearranged in Immature B-cell Tumours," *Nature*, 331, pp. 446-449 (1988)) (copy enclosed as Exhibit F).

None of the specific fragments recited in claims 5-7 render those claims patentably distinct. Accordingly, claim 5-7 are the same patentable invention as Proposed Count 1.

f. Claim 8

Claim 8 recites:

8. A method of claim 3, wherein said transgenic mouse comprises an integrated copy of a NotI insert of pHC1, wherein said transgenic mouse expresses human mu or human gamma-1 chains in serum as a result of isotype switching; each human mu or human gamma-1 chain comprising a variable region having a polypeptide sequence encoded by a human V_H gene segment, a human D segment and a human J_H gene segment, said V_H, D and J_H segments joined in frame.

The method of claim 8 is the same as the method of claim 6, differing only in specifying that the IgG encoded by the transgene is IgG1. The use of IgG1 does not make claim 8 patentably distinct from claim 6. Accordingly, claim 8 corresponds to Proposed Count 1 for the same reasons that claims 3 and 6 do.

h. Claims 9-11

Claims 9-11 correspond substantially to Proposed Count 1. Claims 9-11 recite:

> 9. A method according to claim 3, wherein said transgene further comprises a 5.3 kb HindIII fragment of a human gamma-1 heavy chain gene region, said 5.3 kb HindIII fragment having the human gamma-1 switch region and the first exon of the pre-switch sterile transcript.
>
> 10. A method according to claim 9, wherein the transgene further comprises a 0.7 kb XbaI/HindIII fragment of a human heavy chain region, said 0.7 kb XbaI/HindIII fragment having the sequences immediately upstream of the 5.3 kb human gamma-1 switch region
>
> 11. A method according to claim 10, wherein the transgene further comprises a 3.1 kb XbaI fragment having the sequences immediately upstream of said 0.7 kb XbaI/HindIII fragment of the human heavy chain region.

Claim 9 differs from claim 3 by specifying a particular fragment of a human gamma-1 gene region that includes the gamma-1 switch region and the first exon of the sterile-transcript. The transgene of claim 3 includes a sterile transcript promoter and a human gamma switch region. As discussed, *supra*, use of gamma-1 sequences is within claim 3 and does not confer patentability. The use of the recited DNA fragment does not render claim 9 patentably distinct. Accordingly, claim 9 corresponds to Proposed Count 1 for the same reasons that claim 3 does.

Claims 10 and 11, which depend from claim 9, add restriction fragments with additional upstream sequences. Methods using these sequences are not patentable over the methods of claim 9. Accordingly, claims 10 and 11 correspond to Proposed Count 1 for the reasons that claims 3 and 9 do.

i. Claim 12

Claim 12 corresponds substantially to Proposed Count 1. Claim 12 recites:

> 12. A method according to claim 3, wherein said transgene comprises a human gamma-1 constant region including the associated switch region and sterile transcript associated

exon, together with approximately 4 kb flanking sequences upstream of the sterile transcript initiation site, and a heavy chain 3' enhancer that can be PCR amplified with the following oligonucleotide primers:

5' CAG GAT CCA GAT ATC AGT ACC TGA AAC AGG GCT TGC 3'
5' GAG CAT GCA CAG GAC CTG GAG CAC ACA CAG CCT TCC 3'

The method of claim 12 is substantially the same as the method of claim 11. As in claim 11, claim 12 recites that the transgene comprises a gamma-1 constant region, including switch region, sterile transcript exon and upstream sequences. The transgene of Claim 12 comprises a heavy chain 3' enhancer that can be PCR amplified with a recited oligonucleotide primer. Claim 3 includes the use of a heavy chain 3' enhancer. The use of the recited 3' enhancer does not render claim 12 patentable over claim 3.

Accordingly, claim 12 recites the same patentable invention as claims 3 and 11 and corresponds to Proposed Count 1 for the reasons that those claims do.

1. Claims 13 and 14

Claims 13 and 14 correspond substantially to Proposed Count 1. Claims 13 and 14 recite:

13. A method according to claim 1, wherein said transgene comprises a NotI insert of pHC1 and wherein said transgenic mouse expresses both human mu and human gamma-1 chains in serum.

14. A method according to claim 1, wherein said step of collecting heterologous immunoglobulins comprises collecting a serum containing human gamma-1 chains.

The method of Proposed Count 1 uses a transgene that includes human V, D and J segments, that undergoes isotype switching from a transgene encoded mu isotype to a transgene encoded gamma isotype. Proposed Count 1, thus, includes a transgene containing all of the sequences needed for the expression of both human mu and human gamma immunoglobulins (including gamma-1). In addition, in Proposed Count 1, the transgene has fewer

nucleotides between the mu and gamma segments than are between those segments in the human germline.

Claim 13 specifies a transgene containing the NotI insert of pHC1. As discussed, *supra*, that insert is one embodiment of and, thus, included in the transgene of Proposed Count 1. The particular embodiment of claim 13 is not patentable over the Proposed Count.

Claim 14 recites the method of Proposed Count 1, adding only that gamma-1 immunoglobulins are collected from serum. Neither of those limitations render claim 14 patentable over Proposed Count 1.

Accordingly, claims 13 and 14 correspond to Proposed Count 1.

SUMMARY

As demonstrated above, claim 45 is fully supported in the present application and in the '008 application. It thus is patentable to applicants for the same reasons that claim 1 of the '806 patent was found patentable. Accordingly, an Interference should be declared between claims 1-14 of the '806 patent and claim 45 of this application. The count in interference should be Proposed Count 1. Applicants should be Senior Party based on their January 12, 1990 filing date.

REQUEST FOR SUSPENSION OF PROSECUTION OF OTHER APPLICATIONS RELATED TO THE '806 PATENT

The '860 application, from which the '806 patent issued, was subject to a requirement for restriction. The claims of the '806 patent correspond to one of eleven groups of

claims identified by the Examiner. Divisional applications directed to some or all of remaining groups, and claiming priority from the '860 application (and from the '748 application), may now be pending. In view of the Examiner's restriction, those divisional applications may be directed to:

an immunoglobulin heavy chain transgene;

a transgenic non-human animal;

a hybridoma;

the monoclonal antibody produced by the hybridoma;

a transgenic non-human animal having detectable heterologous antibodies and at least one suppressed endogenous locus;

a method for suppressing an endogenous locus using an antisense transgene;

a method for inactivating an endogenous locus using a targeting vector;

a method for generating an animal with an inactivated immunoglobulin locus by breeding;

an antisense transgene;

a non-human animal having an antisense transgene.

These subject matters are not patentable over claim 1 of the '806 patent or claim 45 of this application. Any patent issuing to applicants on claim 45 from this application, thus, will be "a patent granted on an application for patent by another" having an earlier effective filing date and citable against the divisional applications of the '860 application under 35 U.S.C. § 102(e). Accordingly, prosecution of any divisionals of the '806 patent should be suspended pending the outcome of the requested interference.

In addition, applicants are aware of the following pending applications which claim benefit from the application

from which the '806 patent issued and the earliest filed '748 application:

Serial No. 07/834,539, filed February 5, 1992;

Serial No. 07/853,408, filed March 18, 1992;

Serial No. 07/900,972, filed June 18, 1992;

Serial No. 08/001,493, filed January 7, 1993;

Serial No. 08/053,131, filed April 26, 1993;

Serial No. 08/096,762, filed July 22, 1993;

Serial No. 08/155,301, filed November 18, 1993;

Serial No. 08/161,739, filed December 3, 1993;

Serial No. 08/165,699, filed December 10, 1993; and

Serial No. 08/209,741, filed March 9, 1994.

Applicants believe these applications contain subject matter that conflicts with this application.

For the reasons stated above, prosecution of any applications claiming priority from the '860 or '748 applications and containing subject matter that conflicts with this application should be suspended pending the outcome of the requested interference.

Applicants request entry of the claim, declaration of an interference and suspension of the above-mentioned applications related to the '906 patent.

Respectfully submitted,

1/17/96

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